

# Treatment of Reactions in Solutions with Isodensity Surfaces

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**ABSTRACT:** SINDO1 calculations are performed to study solvation effects on simple intra- and intermolecular reactions. The polarizable continuum model is implemented efficiently with isodensity surfaces. It is demonstrated for the tautomerization of 3-hydroxypyrazole and the Menshutkin reaction that the inclusion of solvation effects is essential for a correct description of the reaction. It is illustrated in the case of the Menshutkin reaction that isodensity surfaces have the necessary flexibility to follow the reaction along the reaction pathway. © 1999 John Wiley & Sons, Inc. *J Comput Chem* 20: 301–304 (1999)

**Keywords:** reactions in solution; isodensity surfaces; solvation effects; SINDO1 calculations

## Introduction

It is well known that the simulation of chemical reactions in the gas phase can be quite deficient if experiments are studied in solution. Solvation effects can be included by a supermolecule approach where one or several solvent molecules are included in the calculation in specific arrangements around the solute molecule or by a continuum model that acts as a perturbation on the solute molecule. We recently extended the scope of our semiempirical molecular orbital method SINDO1 for first-row<sup>1</sup> and second-row<sup>2</sup> elements

by the implementation of the polarizable continuum model (PCM).<sup>3</sup> A fast and precise method for the calculation of solvation energies was achieved<sup>4</sup> based on isodensity surfaces for the cavity surface and on the approximated molecular electrostatic potential (MESP). The implementation of the PCM into SINDO1 in combination with the asymptotic density model<sup>5</sup> provided a significant reduction of computer time for the MESP while retaining its quality. As a new idea we used isodensity surfaces for the calculation of the cavity surfaces because they provide a physical description of molecular surfaces.<sup>6</sup> Subsequently, we tested this model for the change of reactivity of a large number of tetramethylenes and trimethylenes in solution.<sup>7</sup> With our model we could explain the change of diradicals to zwitterions in polar media due to the solvent. This has important implications for the

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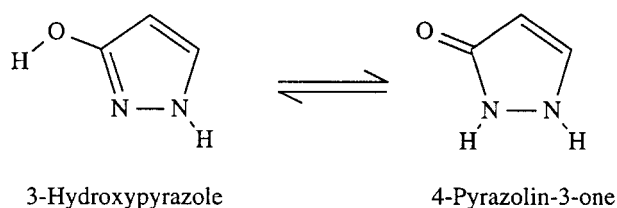
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understanding of the copolymerization and homopolymerization mechanism<sup>8,9</sup> in such systems. In the present work we want to extend the scope of this model further to the study of thermal reactions in solution. In the case of two simple intra- and intermolecular reactions it is demonstrated that solvation effects can be properly accounted for and isodensity surfaces are an efficient means to illustrate the reaction along the reaction pathway.

## Intramolecular Reaction

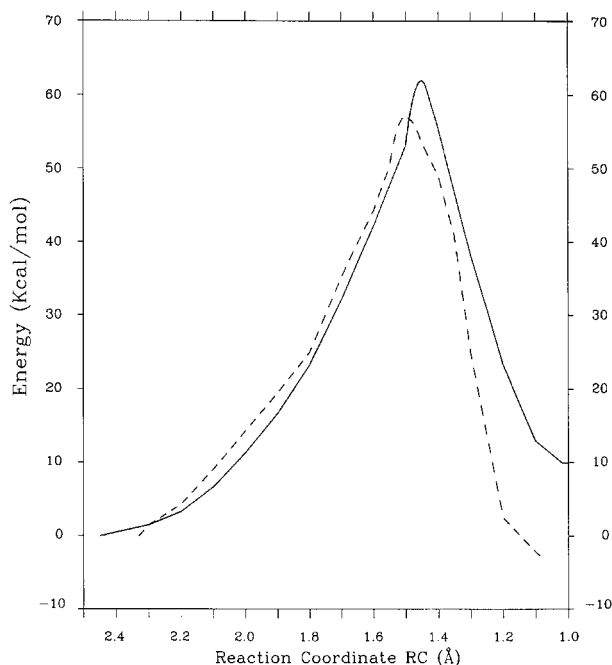
As an example for an intramolecular reaction we present the tautomerization of 3-hydroxypyrazole to 4-pyrazolin-3-one (Fig. 1). In addition to these two tautomers one can think of seven more tautomers. Of these nine compounds five are experimentally important.<sup>10</sup> *Ab initio* calculations predict that 3-hydroxypyrazole is the most stable and 4-pyrazolin-3-one the least stable of the relevant five tautomers in the gas phase.<sup>11</sup> The energy difference is 7.5 cal/mol while AM1 predicts an energy difference of 11.8 kcal/mol.<sup>12</sup> In polar solvents like water, however, 4-pyrazolin-3-one is found to be the most experimentally stable tautomer.<sup>10</sup> From the experiment it is estimated that the energy difference is less than 1.5 kcal/mol in favor of 4-pyrazolin-3-one.<sup>13</sup> In *ab initio* PCM calculations (MP4/6-31G\*\*) 3-hydroxypyrazole was more stable by 3.3 kcal/mol.<sup>13</sup> Here no geometry optimization in solution was attempted. In Monte Carlo calculations 4-pyrazolin-3-one is favored by 3.2 kcal/mol. This is explained by hydrogen bonding, which is not included in the PCM calculations. The sigmatropic rearrangement, a [1,3]-antarafacial hydrogen shift, is allowed by the Woodward-Hoffmann rules,<sup>14</sup> but it involves a large geometry distortion. *Ab initio* calculations predict a barrier of about 50 kcal/mol.<sup>11</sup>

We performed SINDO1 calculations on the self-consistent field level, because it turned out that correlation effects on the CI level were negligible



**FIGURE 1.** Tautomerization of 3-hydroxypyrazole to 4-pyrazolin-3-one.

in SINDO1 for this system. As reaction coordinate  $R_C$  the distance of the migrating hydrogen atom from the nitrogen atom was chosen. The geometry of the reacting system was fully optimized along this reaction coordinate. As in previous calculations<sup>4,7</sup> on solvent effects we chose a cavity that is determined by an isodensity surface of the molecular system. The density value of the isodensity surface was chosen as 0.002 e/bohr<sup>3</sup>. Sjöberg and Politzer<sup>15</sup> showed that this surface includes 95% of the electronic density of some small molecules and that it is physically reasonable. The reaction profile in the gas phase and for solution in water is shown in Figure 2. In the gas phase 3-hydroxypyrazole is more stable than 4-pyrazolin-3-one by 10.2 kcal/mol. In solution the relative stability is reversed in favor of 4-pyrazolin-3-one by 3.4 kcal/mol. The change of relative stability in solution is only observed if the geometry is optimized in solution. If the gas phase geometry for the two tautomers is kept in solution, 3-hydroxypyrazole is more stable by 12.2 kcal/mol. Without proper geometry optimization the change of energy is in the wrong direction. The reaction barrier found by optimization of the transition state along the reaction coordinate is about 62 kcal/mol in the gas phase and 57 kcal/mol in water. The size of the barrier in the gas phase is comparable to the 50

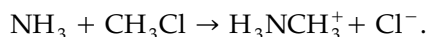


**FIGURE 2.** Reaction profile for rearrangement of 3-hydroxypyrazole to 4-pyrazolin-3-one in the gas phase (—) and in water (---).

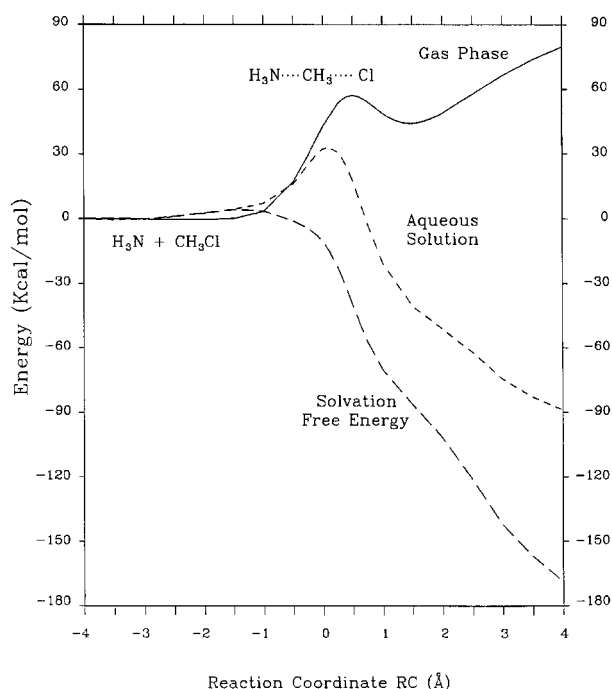
kcal/mol from *ab initio* calculations.<sup>11</sup> The corresponding NH bond length is 1.27 Å compared to 1.33 Å *ab initio*.

## Intermolecular Reaction

We chose the Menshutkin reaction as the intermolecular reaction:

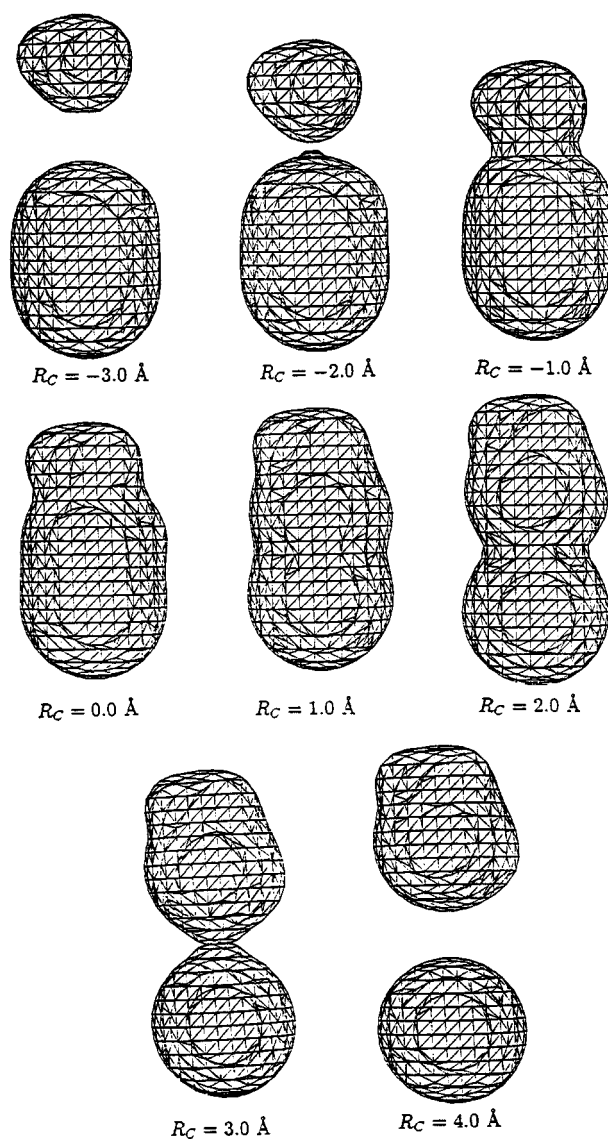


The Menshutkin reaction is an  $S_N2$  reaction where two neutral molecules are converted to two ionic fragments. In the gas phase the reaction is strongly endothermic, whereas the ion pair is stabilized in solution. The reaction barrier of free energy in the gas phase was determined at 46.7 kcal/mol in accurate *ab initio* calculations with an MP4/6-31 + G\* calculation.<sup>16-18</sup> Dillet et al.<sup>19</sup> found almost the same value of  $\Delta G$  for the gas phase reaction with MP2/6-31 + G\*\* *ab initio* calculations (47.5 kcal/mol). The reaction enthalpy ( $\Delta H$ ) was given for the transition state (37 kcal/mol) and the ion pair minimum (30 kcal/mol).<sup>19</sup> Monte Carlo calculations presented a barrier of  $\Delta G = 25.6$  kcal/mol for solution in water.<sup>16,17</sup>



**FIGURE 3.** Reaction profile for the Menshutkin reaction in the gas phase (—) and in water (---).

SINDO1 calculations were performed with an anion correction for chlorine<sup>20</sup> in order to correctly describe the charge separation in the ion pair. The reaction profile of the potential energy for the gas phase and the profile for the free energy in water is shown in Figure 3. The reaction coordinate  $R_C$  is the difference of the C-Cl and C-N bond length. The reaction profiles are in qualitative agreement with the *ab initio* calculations of Gao and Xia<sup>16,17</sup> and Dillet et al.<sup>19</sup> Although the potential energy barrier of the gas phase reaction is obtained at 57.1 kcal/mol in SINDO1, which is about 20 kcal higher than in *ab initio* calculations,<sup>19</sup> the shapes of the



**FIGURE 4.** Cavities for the Menshutkin reaction.

curves are remarkably similar and moreover the stationary points are found at the same location of the reaction coordinate. The ion pair is found to be 44.3 kcal/mol above the reactant. In water the expected stabilization of the ion pair product is clearly pronounced. The barrier of free energy is reduced to 32.4 kcal/mol compared to 28.4 kcal in the *ab initio*.<sup>16</sup> The product is now stabilized compared to the gas phase, which is also predicted in the *ab initio* calculations.

To illustrate the flexibility of isodensity surfaces for calculations in solution we present a series of cavities for various values of the reaction coordinate  $R_C$  along the reaction pathway.

Figure 4 demonstrates that isodensity surfaces can easily follow combination and fragmentation processes during the reaction. First the two cavities of  $\text{NH}_3$  and  $\text{CH}_3\text{Cl}$  approach each other; then they combine to form the transition structure and finally separate again in the ion pair. The continuity achieved by the use of isodensity surfaces during the reaction is an essential process in the treatment of intermolecular reactions in solution.

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## References

1. Nanda, D. N.; Jug, K. *Theor Chim Acta* 1980, 57, 95.
2. Jug, K.; Iffert, R.; Schultz, J. *Int J Quantum Chem* 1987, 92, 265.
3. Miertus, S.; Scrocco, E.; Tomasi, J. *Chem Phys* 1981, 55, 117.
4. Kölle, C.; Jug, K. *J Comput Chem* 1997, 18, 1.
5. Köster, A. M.; Kölle, C.; Jug, K. *J Chem Phys* 1993, 99, 1224.
6. Pappalardo, R. R.; Sanchez-Marcos, E.; Ruiz-Lopez, M. F.; Rinaldi, D.; Rivail, J.-L. *J Phys Org Chem* 1991, 4, 141.
7. Jug, K.; Kölle, C. *J Phys Chem*, in press.
8. Hall, H. K. Jr. *Angew Chem Int Ed Engl*, 1983, 22, 440.
9. Hall, H. K.; Padias, A. B. *Acc Chem Res* 1990, 23, 4.
10. Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic: New York, 1976.
11. Cao, M.; Teppen, B. J.; Miller, D. M.; Pranata, J.; Schäfer, L. *J Phys Chem* 1994, 98, 11353.
12. Karelson, M. M.; Katritzky, A. R.; Szafran, M.; Zerner, M. C. *J Chem Soc Perkin* 1990, 2, 195.
13. Parchment, O. G.; Green, D. V. S.; Taylor, P. J.; Hillier, I. H. *J Am Chem Soc*, 1993, 115, 1993.
14. Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic: New York, 1970.
15. Sjöberg, P.; Politzer, P. *J Phys Chem* 1990, 94, 3959.
16. Gao, J. *J Am Chem Soc* 1991, 113, 7796.
17. Gao, J.; Xia, X. *J Am Chem Soc* 1993, 115, 9667.
18. Gao, J.; Xia, X. In *Structure and Reactivity in Aqueous Solution*, ACS Symposium Series 568; Cramer, C. J.; Truhlar, D. G. Eds.; American Chemical Society: Washington, D. C. 1994; p 212.
19. Dillet, V.; Rinaldi, D.; Bertran, J.; Rivail, J.-L. *J Chem Phys* 1996, 104, 9437.
20. Iffert, R.; Jug, K. *Theor Chim Acta* 1987, 72, 373.